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## **FLT1, PREGNANCY, AND MALARIA: EVOLUTION OF A COMPLEX INTERACTION**

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In *Plasmodium falciparum*-endemic regions, pregnant women are at increased risk from malaria, especially during first pregnancy. Malarial parasites are sequestered in the intervillous space of the placenta <sup>1</sup>, where they multiply and induce an inflammatory reaction. Severe placental inflammation has been correlated with adverse pregnancy outcomes such as fetal growth restriction, still birth, premature delivery, and possibly preeclampsia <sup>2-4</sup>. Women develop antibodies against placental parasites during their first affected pregnancy and thus acquire resistance to infection in subsequent pregnancies <sup>5</sup>. Antibodies that block adhesion of parasites to placental chondroitin sulfate have been associated with increased birth weights in women with chronic malaria <sup>6</sup>.

In this issue of the PNAS, Muehlenbachs et al. provide evidence that a dinucleotide repeat polymorphism in the 3'-UTR of the *fms*-like tyrosine kinase 1 (*FLT1*) gene may be under natural selection in malaria endemic areas because of its effects on adverse outcomes of placental malaria <sup>7</sup>. The authors have previously shown that elevated soluble FLT1 (sFLT1) is associated with chronic placental malaria and gestational hypertension in nulliparous women from the same population <sup>8</sup>. Intriguingly, elevated sFLT1 is also observed in preeclampsia, a hypertensive complication of pregnancy that, like placental malaria, is most prevalent in first pregnancies <sup>9</sup>.

FLT1 is the receptor for vascular endothelial growth factor (VEGF). sFLT1 is a soluble form of the receptor that inhibits VEGF signaling in the vasculature by competing with full-length FLT1 for binding to VEGF. VEGF, in addition to its pro-angiogenic role, is

thought to be a pro-inflammatory cytokine acting via FLT1 on circulating monocytes<sup>10</sup>. Therefore, FLT1 and sFLT1 may have opposing effects on inflammation. The dinucleotide repeat polymorphism studied by Muehlenbachs et al. was shown to affect expression levels of FLT1 in cord blood monocytes: alleles with fewer than 28 repeats (S alleles) were associated with greater expression of FLT1 when compared with alleles with 28 or more repeats (L alleles). Interestingly, SS fetal genotype was also associated with higher levels of sFLT1 in maternal plasma.

Fewer than expected SS infants were born to first-time mothers and this deficiency was most pronounced in the peak malaria season. Moreover, first-time SS mothers reported a higher frequency of prior pregnancy loss than LL mothers (with SL mothers intermediate), but maternal *FLT1* genotype was not associated with history of prior pregnancy loss for multiparous mothers. These data suggest that SS fetuses suffered disproportionate prenatal losses in the presence of placental malaria. There was an interesting interaction between placental malaria and birthweight among first-born offspring. SS offspring had the highest rate of low birth weight (LBW) in the presence of placental malaria, but the lowest rate in its absence. Placental malaria is associated both with intrauterine growth retardation and with preterm delivery<sup>11</sup>, and it will therefore be useful to determine the relative contributions of these factors to the LBW noted in SS infants.

How does SS fetal genotype contribute to the greater incidence of pregnancy loss and LBW in malaria-infected pregnancies? For first-time mothers with placental malaria, SS

fetal genotype was associated with increased expression of inflammatory markers in the placenta and elevated sFLT1 in maternal plasma. If sFLT1 has anti-inflammatory effects, its increased expression may be a response to the greater inflammation of SS placentas rather than a cause of the inflammation. Perhaps, the latter is mediated via effects of S alleles on the expression of full-length FLT1 rather than sFLT1. It will be important to determine how this polymorphism regulates FLT1 vs sFLT1 expression in the placenta and other cell types.

The authors provide compelling evidence of natural selection acting on the FLT1 polymorphism in Tanzania. SS fetuses are subject to higher rates of prenatal loss and lower birth weights in infected pregnancies, but SS infants have heavier birth weights in the absence of placental malaria. Thus, the balance of selective forces should show spatial and temporal variation depending on the incidence of malaria. S and L alleles coexist in most human populations, although their relative frequencies vary markedly. In particular, L alleles are relatively rare in European and indigenous American populations but relatively common in African, East Asian, and Pacific Islander populations <sup>12</sup>. The frequency of L alleles among northern Europeans (> 5%) is higher than that of 'protective' alleles of other malaria-associated polymorphisms. Therefore, placental malaria may help to explain the geographical variation of allele frequencies, but may not be the only selective factor influencing the polymorphism. It will be of great interest to test whether repeat length modifies the phenotype of other inflammatory disorders previously linked to FLT1 signaling <sup>13</sup> and whether FLT1 genotype influences birth weight in other populations.

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